

REMARKS

I. Status of the Claims

Claims 1-15, and 29-31 are pending in this application, with claims 16-28, and 32 cancelled without prejudice or disclaimer. Claim 1 has been amended to recite "a sieving coefficient of 0.1-1.0 in presence of whole blood," and "a sieving coefficient of 0.1 in water." Support for this amendment can be found, for example, in the as-filed specification at page 8, ll. 27-32, and Figure 3b. Claim 2 is amended herein to recite that "the size of the hydrophilic domains are in the range of 20-50 nm." Support for this amendment can be found, for example, in the as-filed specification at page 12, ll. 18-22. Accordingly, no new matter has been added by these amendments.

II. Double Patenting Rejection

The Office rejects provisionally claims 1-15, and 26-31 on the ground of nonstatutory obviousness-type double patenting as "being unpatentable over claims 1, and 3-7 of copending Application No. 10/540,123" to Göhl et al. ("Göhl"). Office Action at 2.

Applicants respectfully disagree. However, Applicants request that the Examiner hold the rejection in abeyance until the indication of otherwise allowable subject matter. Moreover, Applicants respectfully point out that the filing date for the present application is June 17, 2005, which is prior to the filing date of Göhl of June 20, 2005. Thus, "if 'provisional' [obviousness-type double patenting] rejections in two applications are the only rejections remaining in those applications, the Office should withdraw the [obviousness-type double patenting] rejection in the earlier filed application thereby

permitting that application to issue without need of a terminal disclaimer."

M.P.E.P. § 804 I.B.1.

III. Rejections under 35 U.S.C. § 103(a)

A. *Buck* as evidenced by *Gorsuch*

The Office rejects claims 1-11, 13, and 26-29 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Patent No. 4,935,414 to Buck et al. ("Buck") as evidenced by U.S. Patent No. 6,802,820 to Gorsuch et al. ("Gorsuch"). See Office Action at 3-5. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of, *Buck* and *Gorsuch*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

Claim 1, as-amended, recites:

A permselective asymmetric hollow fibre membrane for the separation of toxic mediators from blood, comprised of at least one hydrophobic polymer and at least one hydrophilic polymer, wherein said membrane **allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water.**

As an initial point, the Office has not established that the presently claimed permselective asymmetric hollow fibre membrane and the membrane of *Buck* are identical membranes, as required to show anticipation. Applicants respectfully submit that nowhere does *Buck* teach, suggest, or disclose, *inter alia*, a membrane which allows "passage of molecules passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has

a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water," as recited in claim 1, from which all other pending claims depend. Thus, *Buck* does not anticipate the presently pending claims.

Moreover, "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. § 2141.02(I) (internal citations omitted; emphasis in original). Applicants respectfully submit that after considering *Buck* and *Gorsuch*, the claimed invention as a whole, would not have been obvious.

Buck discloses selectively permeable asymmetric membranes that are "produced from hydrophobic and hydrophilic polymers . . . [with] a three-layered structure including a first dense thin skin layer which includes uniform pores of a size whereby proteins having a molecular weight of at least that of albumin are substantially rejected therefrom, an intermediate second layer in the form of a sponge and having a higher diffusive permeability than the first layer, and a third layer with a finger-like structure which provides mechanical stability. These membranes are preferably formed in the shape of hollow fibers, with the first layer as the inner layer thereof." See Abstract. However, as discussed above, *Buck* does not teach, suggest, or disclose, *inter alia*, a membrane which allows "passage of molecules passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water."

The Office contends that "it is implicit or at least obvious that BUCK allows passage of molecules having a molecular weight of up to 45 kDa," and relies on Figure 7 of *Gorsuch* to support the alleged implied teaching in *Buck*. Office Action at page 3. The Office cites to *In re Aller*, contending that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Office Action at page 3. Applicants respectfully submit, however, that the general conditions of the instant claims are disclosed in the prior art and the Office has not established that the membrane of *Buck* may be modified by "routine experimentation" to have the characteristics recited in the instant claims. For example, *Buck* describes at col. 5, ll. 47-55:

[w]ith the membranes of the present invention, the combination of these two requirements can now be fulfilled, i.e., it is now possible to not only provide a high sieving coefficient (S) of at least about 0.6, e.g., between about 0.6 and 0.8, for β -microglobulin, but at the same time provide a low sieving coefficient for albumin, of about 0.001.

Id. Thus, *Buck* teaches that for smaller compounds (i.e., β -microglobulin having a molecular weight of 11,500 Daltons), the sieving coefficient ranges from 0.6 to 0.8. However, the instantly claimed membrane "allows passage of molecules having a molecular weight of up to 45,000 Daltons with a sieving coefficient of 0.1-1.0." It is clear, therefore, that *Buck*'s membrane is different from the instant membrane. Moreover, nowhere does *Buck* suggest that it would be desirable to have a membrane with the instant characteristics, much less that its membrane may be, or could be modified to obtain a sieving coefficient as presently claimed.

Additionally, according to Figure 7 of *Gorsuch*, the membrane disclosed therein would have a sieving coefficient during hemofiltration lower than 0.1 for molecules having a molecular weight of about 45,000 Daltons. In contrast, the instant membrane "allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood." This indicates that the membrane in Figure 7 of *Gorsuch* is more dense than the membrane according to the invention and would allow passage of molecules having a molecular weight of about 45,000 Daltons to a lesser degree than the instant membrane. This is clear when the relative pore sizes of membrane in Figure 7 of *Gorsuch* and the pore sizes of the instant membrane are compared. According to Figure 7 of *Gorsuch*, the figure is for "membranes with pores in the .006 to .009 µm diameter size for ultrafiltration." See caption for curve 11 in Figure 7 of *Gorsuch*. In contrast, the presently claimed membrane has three layers, with the pore sizes of each layer not being necessarily the same to each other. For example, the pores of the innermost layer of a membrane according to the invention have pore sizes ranging from "15-60nm," or .015-.060 µm. See page 9, ll. 28-33 of the as-filed specification. These differences highlight the fact that the membrane of Figure 7 of *Gorsuch* has characteristics and properties different from those of the membranes of the invention and that *Gorsuch* fails to support the Office's contention that *Buck* "implicitly" meets the limitation of the instant claims.

Further, the Office states that "[i]t is inherent that the hollow fiber membrane has a molecular weight exclusion limit in water of about 200 kDa, absent evidence to the contrary." Office Action at page 3. Applicants respectfully disagree. The burden is initially on the Office to show, in the present case, that the membrane of *Buck*

necessarily exhibits the molecular weight exclusion of the claimed membrane in water.

M.P.E.P. § 2112.01 It is well settled that before shifting the burden of proof to Applicants, the Office is required to "present evidence or reasoning tending to show inherency." M.P.E.P. § 2112.V. That is, "[i]n relying upon the theory of inherency, the Office *must* provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112.IV (emphasis added). The Office has not met this burden. The Office has not provided a single "basis in fact and/or technical reasoning" to show how *Buck* necessarily exhibits the molecular weight exclusion limit in water of about 200 kDa recited in the claims. Furthermore, *Gorsuch* fails to describe how the membrane performs with aqueous protein solutions. Thus, the Office's statement that "[i]t is inherent that the hollow fiber membrane has a molecular weight exclusion limit in water of about 200 kDa," is overly conclusory, unsupported by any facts or reasoning, and contrary to the guidelines of the M.P.E.P.

For the forgoing reasons, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of anticipation or obviousness over the combination of, *Buck* and *Gorsuch*. Accordingly, Applicants respectfully request withdrawal of this rejection.

B. *Kawata* as evidenced by *Gorsuch*

The Office rejects claims 1-11, 13-14, 26-29, and 30 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being

unpatentable over EP 0 568 045 to Kawata et al. ("Kawata")¹ as evidenced by Gorsuch. See Office Action at 5-7. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of, Kawata and Gorsuch, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

Kawata, like Buck, does not anticipate the pending claims for at least the reason that the Office has failed to establish that each and every element recited in, for example, independent claim 1 is disclosed by Kawata. As Kawata fails to disclose a membrane which allows "passage of molecules passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water," Kawata fails to anticipate the pending claims.

Moreover, Kawata discloses a sieving coefficient of 0.001 for albumin (see, e.g., Table 1), which indicates that the pores in Kawata's membrane are even smaller than those of Buck. Consequently, just like Buck, it is clear that Kawata's membrane is very different from the membranes of the instant invention.

Further, the Office cites to Kawata as disclosing "a hollow fiber membrane with an asymmetric structure . . . where it is implicit that the polymers are present as domains on the surface, absent evidence to the contrary." *Id.* at page 5. Applicants respectfully disagree. As mentioned above, it is the Office's burden to show inherency

¹ Applicants note that the Office refers to Kagawa as the first named inventor for EP 0 568 045. However, Kawata is the first named inventor on EP 0 568 045, and Applicants will refer to EP 0 568 045 by "Kawata" herein.

by providing "a basis in fact and/or technical reasoning" before shifting the burden to Applicants. The Office has not met this burden. For at least this reason, the Office has failed to show a *prima facie* case of anticipation and/or obviousness in the instant rejection.

The Office again cites to *Gorsuch* as evidence that the membrane of *Kawata* necessarily allows passage of molecules having a molecular weight of up to 45kDa. See Office Action at pages 5-6. However, as explained above, *Gorsuch's* Figure 7 is based on a membrane with pore size diameter in the .006 to .009 μm range. See caption. The results in Figure 7 cannot be applied to the *Kawata's* membrane because *Kawata* teaches that its claimed membranes "have many micropores of a 0.05-1 μm pore diameter." *Id.* at page 10, ll. 44-46. Thus, the measurement conditions for curve 11 in Figure 7 of *Gorsuch*, which are relevant to the membrane with pore size diameter in the .006 to .009 μm range, fall outside the pore size diameter for the membrane disclosed in *Kawata*. As such, *Gorsuch* does not apply to *Kawata*, much less to the presently pending claims.

For the foregoing reasons, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of anticipation or obviousness over the combination of, *Kawata* and *Gorsuch*. Accordingly, Applicants respectfully request withdrawal of this rejection.

C. *Gorsuch*

The Office rejects claims 1-2, 5-7, and 26-28 under 35 U.S.C. § 102(e) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over *Gorsuch*. See Office Action at 7-8. Applicants respectfully disagree

and submit that the rejected claims are neither anticipated by, nor obvious *Gorsuch*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

Gorsuch does not anticipate the pending claims for at least the reason that the Office has failed to establish that each and every element recited in, for example, independent claim 1 is disclosed by *Gorsuch*. As *Gorsuch* fails to disclose a membrane which allows “passage of molecules passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water,” it cannot be said that *Gorsuch* anticipates the pending claims.

The Office states that *Gorsuch* “discloses a permselective asymmetric hollow fiber membrane . . . where it is implicit that the hydrophobic and hydrophilic polymer are present as domains on the surface, absent evidence to the contrary” *Id.* at page 7. Here, the Office improperly interprets the disclosure of *Gorsuch* as disclosing a membrane with hydrophobic and hydrophilic polymers present as domains on the surface. *Gorsuch* explicitly teaches at col. 4, ll. 41-44, that “[t]he membranes of the present invention may be prepared using any suitable polymer fibers which will result in a hollow fiber membrane which meets the biocompatibility requirements' and properties of the invention.” *Id.* (emphasis added). Contrary to the Office's opinion, *Gorsuch* implies that any suitable polymer fiber would be appropriate for the membrane disclosed therein, as long as it is it “meets the biocompatibility requirements' and properties of the invention.” Accordingly, nowhere in *Gorsuch* is it implied that the membranes disclosed therein are comprised of specifically at least one hydrophobic and at least one

hydrophilic monomer, much less that the membranes disclosed therein are composed of hydrophobic and hydrophilic domains.

Moreover, as explained above, the measurement conditions for curve 11 of Figure 7 of *Gorsuch* are not applicable the presently pending claims, as the pore size diameters are different from those of the present membrane. Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of anticipation or obviousness over *Gorsuch*. Accordingly, Applicants respectfully request withdrawal of this rejection.

D. Buck as evidenced by Herbelin

The Office rejects claim 12 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over *Buck* as evidenced by Herbelin et al. *Elevated circulating levels of interleukin-6 in patients with chronic renal failure*, Kidney International, Vol. 39, (1991), pp. 954-960 ("Herbelin"). See Office Action at page 9. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of, *Buck* and *Herbelin*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

As discussed above, *Buck* neither anticipates, nor renders obvious the presently pending claims. According to the Office, *Buck* "discloses sieving coefficients for various blood components (C5/L46-54), where it is inherent that the sieving coefficient for IL-6 in presence of whole blood is 0.9-1.0 based on the molecular weight of IL-6 (approximately 26 kDa)" *Id.* at page 9. Applicants respectfully disagree, and submit that the Office is again mischaracterizing *Buck*. *Buck* describes at col. 5, ll. 46-

54 that the sieving coefficient of β -microglobulin (MW 11,500 Daltons) for the membrane disclosed therein ranges from 0.6-0.8. *See id.* Thus, *Buck* discloses a sieving coefficient range from 0.6-0.8 for a molecule with a lower molecular weight than that of IL-6 (MW 26,000 Daltons). It is, therefore, clear that *Buck* cannot inherently teach a higher sieving coefficient (0.9-1.0) for a molecule with a higher molecular weight, such as IL-6. If anything, *Buck* implies that the sieving coefficient for a higher molecular weight molecule (i.e., IL-6) would be lower than the sieving coefficient disclosed for β -microglobulin, and not higher as the Office proffers.

Herbelin fails to remedy the deficiencies of *Buck*. Accordingly, the Office has failed to establish a *prima facie* case of anticipation, or obviousness over the combination of, *Buck* and *Herbelin*, and thus respectfully request withdrawal of this rejection.

E. Kawata as evidenced by Herbelin

The Office rejects claim 12 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over *Buck* as evidenced by *Kawata* as evidenced by *Herbelin*. *See* Office Action at pages 9-10. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of *Kawata* and *Herbelin*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

As discussed above, *Kawata* neither anticipates, nor renders obvious the presently pending claims. According to the Office, *Kawata* "discloses that the hollow fiber membranes have a high sieving co-efficient for middle molecules . . . where it is implicit that the sieving [sic] co-efficient for IL-6 . . . is 0.9-1.0." *Id.* at page 10.

Applicants respectfully disagree. *Kawata* neither explicitly, nor implicitly, discloses that the membrane therein would have a sieving coefficient for IL-6 of between 0.9-1.0. As mentioned above, it is the Office's burden to show inherency by providing "a basis in fact and/or technical reasoning" before shifting the burden to Applicants. The Office has not met this burden. For at least this reason, the Office has failed to show a *prima facie* case of anticipation and/or obviousness in the instant rejection.

Again, *Herbelin* fails to remedy the deficiencies of *Kawata*. Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of anticipation or obviousness over the combination of *Kawata* and *Herbelin*, and thus respectfully request withdrawal of this rejection.

F. Gorsuch as evidenced by Herbelin

The Office rejects claim 12 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over *Buck* as evidenced by *Gorsuch* as evidenced by *Herbelin*. See Office Action at pages 10-11. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of, *Gorsuch* and *Herbelin*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

The Office fails to provide any evidence in the Office Action that the membrane of *Gorsuch* would necessarily have a sieving coefficient for IL-6 ranging from 0.9-1.0, but rather contends in a conclusory manner, that "it appears that the sieving co-efficient of IL-6 would be 0.9-1.0." *Id.* at page 10. According to Figure 7 of *Gorsuch*, IL-6, which for present purposes is assumed to have a molecular weight of about 20,000-30,000 Daltons, would result in a sieving coefficient of about less than 0.2, which is much lower

than the 0.9-1.0 range alleged by the Office. Thus, Applicants respectfully disagree and submit that the rejected claims are neither anticipated by, nor obvious over the combination of, *Gorsuch* and *Herbelin*, and request reconsideration and withdrawal of the rejection for the reasons outlined below.

As discussed above, *Gorsuch* neither anticipates, nor renders obvious the presently pending claims. *Herbelin* fails to remedy the deficiencies of *Gorsuch*. Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of anticipation or obviousness over the combination of, *Gorsuch* and *Herbelin*, and thus respectfully request withdrawal of this rejection.

H. Buck as evidenced by Kawata and Gorsuch

The Office rejects claims 14-15, and 30-31 under 35 U.S.C. § 102(b) as anticipated by or in the alternative, under 35 U.S.C. § 103(a), as allegedly being unpatentable over *Buck* as evidenced by *Kawata* and *Gorsuch*. See Office Action at pages 11-13. Applicants respectfully disagree because the rejected claims are neither anticipated by, nor obvious over the combination of, *Buck*, *Kawata*, and *Gorsuch*, and request reconsideration and withdrawal of the rejection for at least the reason that claims 14-15, and 30-31 ultimately depend upon independent claim 1, and as discussed above, none of these references alone or in combination with each other anticipate nor renders obvious claim 1. For at least this reason, Applicants respectfully request withdrawal of the rejection.

VI. Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully requests the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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